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EUROPEAN UROLOGY XXX (2019) XXX–XXX

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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Improved Prostate Cancer Biopsy Grading by Incorporation of Invasive Cribriform and Intraductal Carcinoma in the 2014 Grade Groups

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Article info

Article history:
Accepted July 31, 2019

Associate Editor:
Matthew Cooperberg

Statistical Editor:
Melissa Assel

Keywords:
Cribriform
Gleason score
Grade
Intraductal carcinoma
Prostate cancer

Abstract

Background: Grade groups (GGs) are an important parameter for therapeutic decision making in prostate cancer (Pca) patients. Invasive cribriform and/or intraductal carcinoma (CR/IDC) has an independent prognostic value for disease outcome, but are not included in the GG limiting their clinical use.
Objective: To perform a proof-of-principle study incorporating CR/IDC in the current GG.
Design, setting, and participants: All prostate biopsies of 1031 men with screen-detected Pca between 1993 and 2000 were reviewed for the current GG (ranging from 1 to 5) and CR/IDC. The cribriform grade (cGrade) was equal to the GG if CR/IDC was present and GG minus 1 if not. GG1 was cGrade1 if intraductal carcinoma was absent.
Intervention: Biopsy review for GG and CR/IDC. A total of 406 patients had received radical prostatectomy (RP), 508 radiotherapy (RT), 108 surveillance, and eight hormonal therapy, and the treatment was unknown for one patient.

Outcome measurements and statistical analysis disease-specific survival (DSS), metastasis-free survival (MFS), and biochemical recurrence–free survival (BCRFS) after 15.1 yr (interquartile range 10.9–19.7 yr) follow-up were compared using Harrell's C-statistic.
Results and limitations: The biopsy GGs were 486 GG1, 310 GG2, 104 GG3, 64 GG4, and 67 GG5; cGrade distributions were 738 cGrade1, 102 cGrade2, 91 cGrade3, 58 cGrade4, and 42 cGrade5. The cGrade had a better discriminative value than the GG for DSS (C-index 0.79; 95% confidence interval 0.74–0.83 vs 0.76; 0.71–0.82) and MFS (0.79; 0.74–0.84 vs 0.77; 0.72–0.82). The discriminative value for BCRFS after RP and RT was similar for both models. Different diagnostic, such as use of sextant biopsies, and therapeutic strategies in the 1990s are the limitations of this study.
Conclusions: The cGrade is a simple Pca grade modification with better discriminative values for DSS and MFS than the GG, particularly impacting decision making in men with current GG2 Pca.
Patient summary: Microscopic grading is an important factor for decision making in prostate cancer (Pca) patients. We show that a simple grade modification better predicts Pca outcome and might improve treatment choices.

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https://doi.org/10.1016/j.eururo.2019.07.051
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Please cite this article in press as: van Leenders GJLH, et al. Improved Prostate Cancer Biopsy Grading by Incorporation of Invasive Cribriform and Intraductal Carcinoma in the 2014 Grade Groups. Eur Urol (2019), https://doi.org/10.1016/j.eururo.2019.07.051

1. Introduction

The Gleason grading system is one of the most important parameters for clinical decision making in prostate cancer (Pca) patients. Gleason score (GS) is entirely based on pathological assessment of tumour growth patterns and takes into account tumour heterogeneity. While the system was first developed in the late 1960s, it has been modified several times over the years and is currently based on the 2014 consensus conference of the International Society of Urologic Pathology (ISUP) [1,2].

Although the Gleason grading system has been established for several decades, it has a few weaknesses. Firstly, the GS ranges between 2 and 10, which might give patients with GS 6 a false impression to have a tumour of intermediate grade. Secondly, the clinically important distinction between GS 3 + 4 and GS 4 + 3 is not clearly reflected by GS 7 [3]. To overcome these weaknesses, Pierorazio and colleagues [4] introduced "grade groups" (GGs), which are defined as follows: GG1 (GS $\leq$ 6), GG2 (GS 3 + 4 = 7), GG3 (GS 4 + 3 = 7), GG4 (GS 8), and GG5 (GS9–10). The GGs were endorsed by the ISUP and the World Health Organization (WHO), and should be reported in conjunction with the GS [1,2].

In recent years, much evidence was obtained that invasive cribriform and/or intraductal carcinoma (CR/IDC) are pathological features with strong independent predictive values for disease-specific survival (DSS), biochemical recurrence–free survival (BCRFS), and adverse pathological parameters at radical prostatectomy (RP) [5–10]. Patients with biopsy GG2 Pca with presence of CR/IDC show significantly shorter DSS and BCRFS than those without [8,9]. On the contrary, DSS and BCRFS of biopsy GG2 Pca patients without CR/IDC are not statistically different from those of men with GG1 Pca [8,9]. Furthermore, patients with biopsy GG1 Pca with concomitant intraductal carcinoma often show aggressive features at subsequent RP with extraprostatic expansion in up to 64% of cases [11]. Although invasive cribriform Gleason pattern 4 and intraductal carcinoma are strictly two separate pathological entities, they show significant morphological overlap and often coincide. Despite the accumulating evidence of their additional prognostic impact, presence of CR/IDC is not included in the current grading system. This limits their comprehensive and simple incorporation in clinical decision models.

In the current proof-of-principle study, we investigate a modified Pca grading model for prostate biopsies—cribriform grade (cGrade)—which incorporates CR/IDC in the established GG system.

2. Patients and methods

2.1. Patient selection

We identified all 1078 men from the first screening round of the Dutch part of the European Randomized Study of Screening for Prostate Cancer (ERSPC), who had been diagnosed with Pca between November 1993 and March 2000 at the Erasmus University Medical Centre, Rotterdam, The Netherlands [12]. The ERSPC is an ongoing multicentre randomised screening trial that was initiated in the early 1990s to evaluate the effect of screening with prostate-specific antigen (PSA) testing on disease-specific mortality rates. Exclusion criteria of the present study were unavailability of slides or paraffin blocks for review (n = 24) and presence of lymph node or distant metastasis at the time of diagnosis (n = 23), leaving 1031 patients for analysis. The study was approved by the institutional Medical Research Ethics Committee (MEC-2018-1614) and in concordance with the Declaration of Helsinki.

2.2. Pathological evaluation

Three investigators (C.K., I.K., and G.v.L.), who were blinded to patient information and outcome, revised all available histopathological slides (n = 1031) according to the 2014 WHO/ISUP recommendations [2]. For each biopsy core, we recorded GS, GG, presence of CR/IDC, and percentage Gleason pattern 4 [13]. Invasive cribriform structures were defined as both small and expansive malignant epithelial proliferations with intercellular lumina, in which the majority of tumour cells did not contact surrounding stroma and which spanned at least half of the glandular lumen. Intraductal carcinoma was diagnosed according to the WHO criteria [1]. Basal cell immunohistochemistry was performed to differentiate invasive cribriform from intraductal carcinoma in case this was not evident by histopathological parameters alone [9]. Since invasive cribriform and intraductal carcinoma show significant morphological overlap and both have added clinical values, we combined both patterns into one group (CR/IDC). The worst biopsy GG was used for statistical analyses.

2.3. Cribriform grade

The cGrade was conceived as a modification of the GG system and was determined as follows (Supplementary Fig. 1). For Pca patients with GG2–5, the cGrade is similar to the GG if CR/IDC is present. The cGrade is equal to the GG minus 1, if CR/IDC is absent. For men with GG1, the cGrade is 1. In the rare case of GG1 Pca with concomitant intraductal carcinoma, the assigned cGrade is 2.

2.4. Clinical follow-up

After diagnosis and initial treatment, patients were monitored semiannually by a chart review to assess potential progression and secondary treatments. DSS was defined as the time from diagnosis to death attributed to Pca and was evaluated by an independent causes of death committee [12]. Metastasis-free survival (MFS) was defined as the time from diagnosis to the development of distant metastasis or censoring. Biochemical recurrence was defined as a PSA level of $\geq$0.2 ng/ml assessed at two consecutive time points $>$3 mo apart after RP or any PSA increase of $>$2 ng/ml higher than the PSA nadir value after radiotherapy (RT) [14]. BCRFS was defined as the time from RP or the start of RT to biochemical recurrence or censoring.

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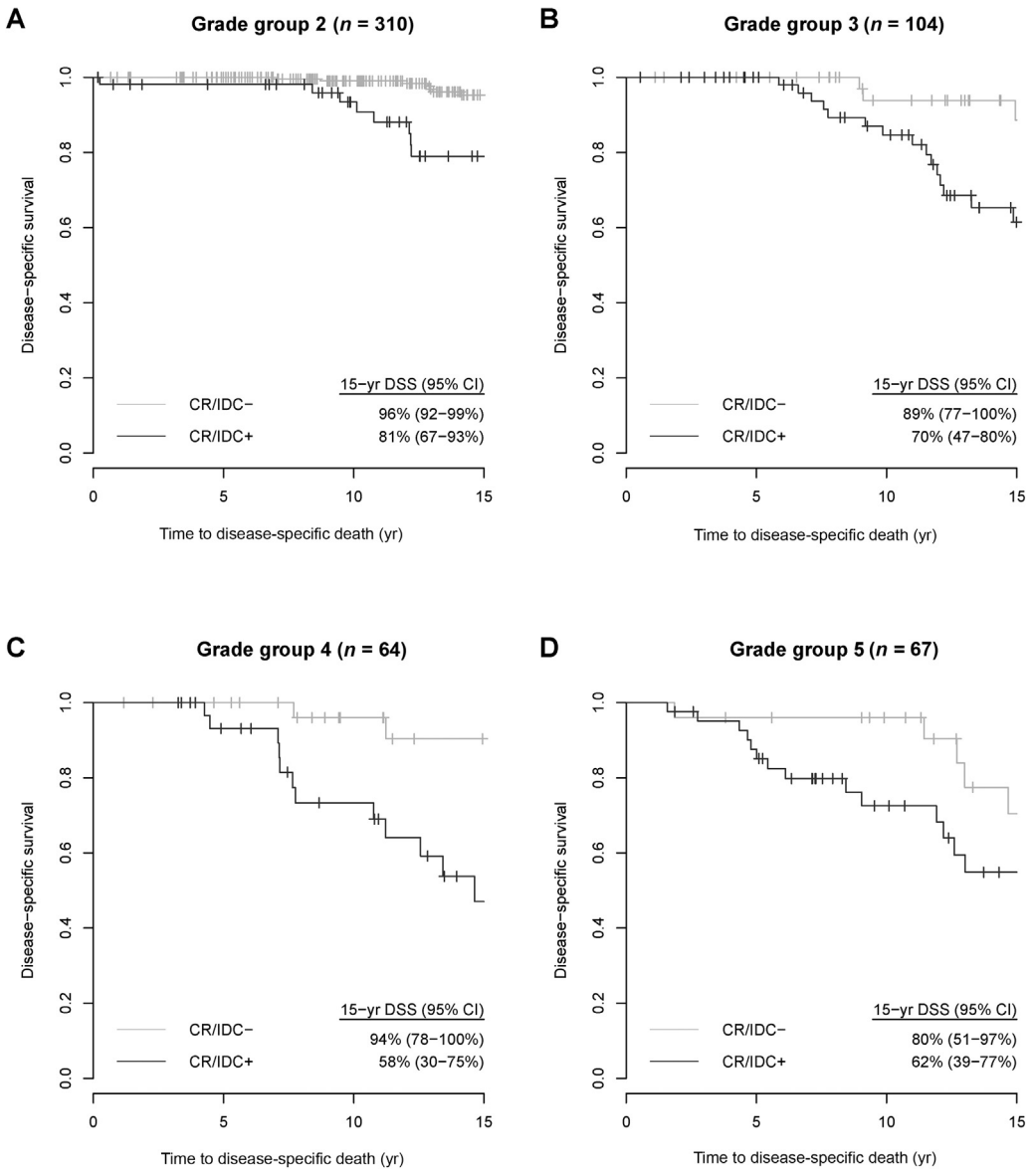

Fig. 1 – Kaplan-Meier survival probabilities of Pca patients stratified for the presence or absence of CR/IDC in (A) grade group (GG) 2, (B) GG3, (C) GG4, and (D) GG5.
CI = confidence interval; CR/IDC = invasive cribriform and/or intraductal carcinoma; DSS = disease-specific survival; Pca = prostate cancer.

2.5. *Statistical analysis*

For DSS and BCRFS analyses, both GG and cGrade were included in five categories (GG1–5 and cGrade1–5), and percentage Gleason pattern 4 was included as a continuous variable. Hazard ratios (HRs) for survival time were calculated using univariable Cox proportional hazard regression. To adjust for different treatments, we included a stratified baseline hazard for treatment and estimated common HR for GG and cGrade. Survival probabilities were plotted using Kaplan-Meier curves. Discriminative ability for grading models was quantified using Harrell's C-index. All statistical analyses were performed in SPSS version 24 (IBM, Chicago, IL, USA) and R version 3.2.2 (R, Vienna, Austria). Two-sided p values of <0.05 were considered statistically significant.

3. Results

3.1. *Patient characteristics*

Our study cohort contained 1031 screen-detected Pca patients (Table 1). Their median age at the time of diagnosis was 67 yr (interquartile range [IQR] 62–71 yr) and the median PSA level was 5.6 ng/ml (IQR 3.9–8.8 ng/ml). In total, 549 (53.3%) men received six biopsies, 460 (44.6%) seven biopsies, and 22 (2.1%) eight biopsies. Four hundred and six (39.2%) patients underwent RP, 508 (49.0%) underwent RT,

Table 1 – Patient characteristics of the study population.

	GS ≤ 6 GG1 (*n* = 486)	GS 3 + 4 = 7 GG2 (*n* = 310)	GS 4 + 3 = 7 GG3 (*n* = 103)	GS 8 GG4 (*n* = 64)	GS 9–10 GG5 (*n* = 67)
Age, median (IQR)	66 (61–70)	67 (62–71)	69 (65–72)	69 (66–72)	67 (64–71)
PSA, median (IQR)	4.7 (3.5–6.9)	5.8 (4.0–9.0)	7.4 (4.7–14.9)	11.0 (6.1–17.4)	9.4 (5.3–16.3)
CR/IDC, *n* (%)	4 (0.8)	54 (17.4)	60 (57.7)	33 (51.6)	42 (62.7)
Radical prostatectomy, *n* (%)	216 (44.4)	129 (41.6)	33 (32.0)	14 (21.9)	14 (20.9)
Radiation therapy, *n* (%)	188 (38.7)	154 (49.7)	66 (64.1)	48 (75.0)	52 (77.6)
Active surveillance/WW, *n* (%)	80 (16.5)	23 (7.4)	3 (2.9)	1 (1.6)	1 (1.5)
Hormonal therapy, *n* (%)	2 (0.4)	3 (1.0)	2 (1.9)	1 (1.6)	0
Unknown, *n* (%)	0	1 (0.3)	0	0	0

CR/IDC = invasive cribriform and/or intraductal carcinoma; GG = grade group; GS = Gleason score; IQR = interquartile range; PSA = prostate-specific antigen; WW = watchful waiting.

108 (10.5%) were under watchful waiting/active surveillance, and eight (0.8%) received hormonal therapy. Primary treatment was unknown in one (0.1%) patient. The median follow-up of patients being alive at the last follow-up was 15.1 yr (IQR 10.9–19.7 yr).

The biopsy grade distribution was as follows: 486 Pca cases were graded as GG1 (GS ≤ 6), 310 cases as GG2 (GS 3 + 4 = 7), 104 cases as GG3 (GS 4 + 3 = 7), 64 cases as GG4 (GS 8), and 67 cases as GG5 (GS 9 or 10). A total of 566 (54.9%) men died during follow-up, 90 (8.7%) of whom died from Pca. Disease-specific death occurred in 2.1% (10/486) of patients diagnosed with biopsy GG1, 6.5% (20/310) with GG2, 22.1% (23/104) with GG3, 25.0% (16/64) with GG4, and 31.3% (21/67) with GG5 Pca.

3.2. Cribriform growth and/or intraductal carcinoma and DSS

Four (0.8%) GG1 (GS ≤ 6) Pca patients had concomitant intraductal carcinoma of the prostate. CR/IDC was observed in 54 (17.4%), 60 (57.7%), 33 (51.6%), and 42 (62.7%) patients with GG2, GG3, GG4, and GG5 Pca, respectively (Fig. 1). In multivariable analysis including the five GG categories, biopsy CR/IDC had additional predictive values for DSS (HR 3.8; 95% confidence interval [CI] 2.3–6.3; $p < 0.001$) and MFS (HR 3.7; 95% CI 2.2–6.2; $p < 0.001$). Adding an interaction between GG and CR/IDC did not lead to a significantly better model fit for DSS ($p = 0.8$) or MFS ($p = 0.6$). Of interest, DSS of men with biopsy GG2 Pca without CR/IDC was not different from the DSS of those with GG1 Pca (HR 1.9; 95% CI 0.8–4.7; $p = 0.15$). While percentage Gleason pattern 4 has also been recognised as a parameter for clinical stratification of GG2 Pca patients, it did not have a predictive value for DSS (HR 1.5; 95% CI 0.03–73.7; $p = 0.8$) or MFS (HR 1.4; 95% CI 0.03–64.1; $p = 0.9$) as a continuous variable in our cohort [1,5,15].

3.3. Cribriform grade modification

Distribution of cGrade among the 1031 patients was as follows: 738 patients were graded as having cGrade1, 102 as cGrade2, 91 as cGrade3, 58 as cGrade4, and 42 as cGrade5 Pca (Table 2). Incorporation of CR/IDC in the cGrade had the most prominent effect in GG2 tumours, of which 256/310 (82.6%) were classified as cGrade1. Reclassification occurred in 42.3% (44/104), 48.4% (31/64), and 37.3% (25/67) of GG3, GG4, and GG5 Pca cases, respectively. Only four out of 486 patients with GG1 Pca (0.8%) were upgraded to cGG2 due to the presence of intraductal carcinoma.

Table 2 – Distribution and relation of grade groups (GGs) and cribriform grade (cGrade).

	GG1	GG2	GG3	GG4	GG5	Total
cGrade1	482	256	–	–	–	738
cGrade2	4	54	44	–	–	102
cGrade3	–	–	60	31	–	91
cGrade4	–	–	–	33	25	58
cGrade5	–	–	–	–	42	42
Total	486	310	104	64	67	1031

3.4. DSS and MFS

Both grading systems were strongly associated with clinical outcome (Table 3). The discriminative value of the cGrade (C-index 0.79; 95% CI 0.74–0.83) in predicting DSS was significantly ($p = 0.029$) higher than that of the GG (C-index 0.76; 95% CI 0.71–0.82; Fig. 2). The cGrade model (C-index 0.79; 95% CI 0.74–0.84) also showed better discrimination than the GG model (C-index 0.77; 95% CI 0.72–0.82) for MFS, although this did not meet conventional measures of statistical significance ($p = 0.062$).

3.5. Biochemical recurrence–free survival

Of the 406 patients who had undergone RP, 216 (53%) had GG1, 129 (32%) GG2, 33 (8%) GG3, 14 (3%) GG4, and 14 (3%) GG5 Pca. Conversion to the proposed cGrade distribution resulted in 326 patients (80%) having cGrade1, 34 (8%) cGrade2, 27 (7%) cGrade3, 12 (3%) cGrade4, and seven (2%) cGrade5 Pca. In total, 85 (20.9%) patients experienced biochemical recurrence after a median of 4.5 yr (IQR 2.3–9.3 yr). Both grading models were strongly associated with postoperative BCRFS (Table 4). There was no significant difference ($p = 0.4$) between the discriminative values of the cGrade model (C-index 0.65; 95% CI 0.58–0.71) and the GG model (C-index 0.65; 95% CI 0.59–0.71).

In total, 223 out of 508 patients who received RT (43.9%) experienced biochemical recurrence after a median

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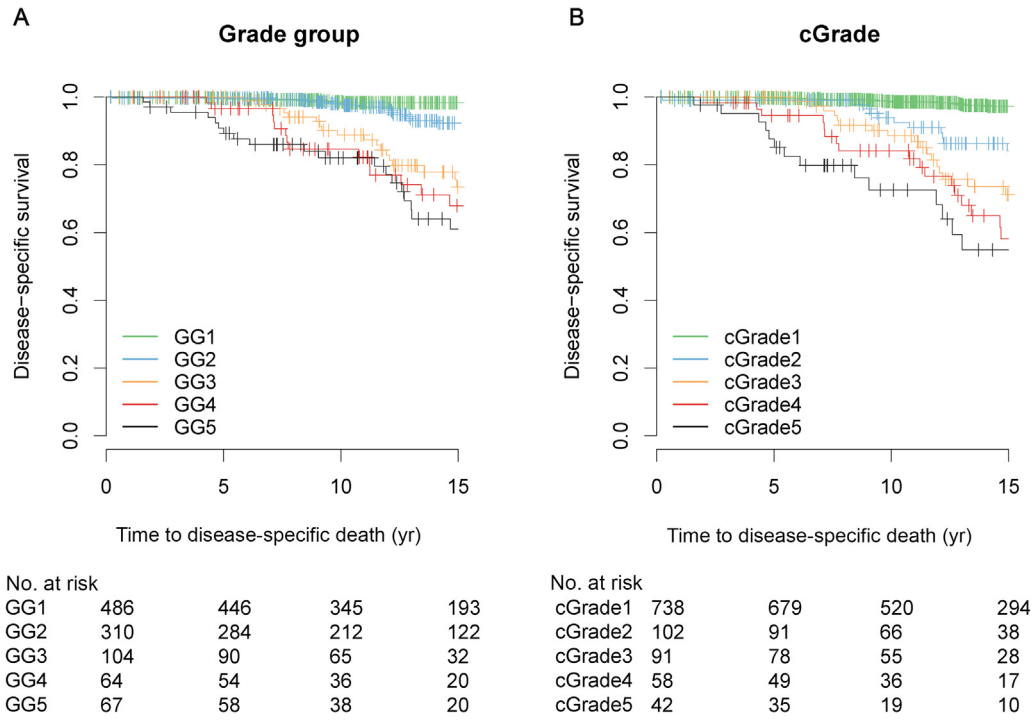

Fig. 2 – Kaplan-Meier survival probabilities of Pca patients graded according to the (A) current grade group model and (B) proposed cGrade model. cGrade = cribriform grade; GG = grade group; Pca = prostate cancer.

Table 3 – Cox proportional hazard models for prostate cancer disease-specific survival and metastasis-free survival stratified by grade groups (GGs) and cribriform grade (cGrade).

Group	Disease-specific survival				Metastasis-free survival			
	Grade group		cGrade		Grade group		cGrade	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
1	ref	–	ref	–	ref	–	ref	–
2	3.1 (1.4–6.6)	0.003	4.6 (2.3–9.1)	<0.001	3.8 (1.7–8.4)	<0.001	3.7 (1.8–7.7)	<0.001
3	10.3 (4.8–22.2)	<0.001	8.4 (4.5–15.8)	<0.001	10.4 (4.6–23.3)	<0.001	9.3 (5.0–17.2)	<0.001
4	11.9 (5.3–26.7)	<0.001	11.2 (5.9–21.4)	<0.001	16.7 (7.3–38.3)	<0.001	12.1 (6.4–23.0)	<0.001
5	16.4 (7.5–35.8)	<0.001	17.9 (9.1–35.2)	<0.001	18.0 (7.9–40.9)	<0.001	15.6 (7.8–31.2)	<0.001

CI = confidence interval; HR = hazard ratio; ref = reference.

Table 4 – Cox proportional hazard models for biochemical recurrence-free survival after radical prostatectomy and radiation therapy stratified by Grade groups (GG) and cribriform Grade (cGrade).

Group	BCRFS after radical prostatectomy				BCRFS after radiation therapy			
	Grade group		cGrade		Grade group		cGrade	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
1	ref	–	ref	–	ref	–	ref	–
2	2.1 (1.2–3.5)	0.006	2.2 (1.1–4.4)	0.02	1.9 (1.3–2.8)	0.001	2.5 (1.7–3.7)	<0.001
3	4.1 (2.1–7.8)	<0.001	4.4 (2.4–7.9)	<0.001	4.4 (2.9–6.7)	<0.001	4.4 (3.0–6.5)	<0.001
4	5.0 (2.2–11.6)	<0.001	4.5 (1.9–10.4)	0.001	5.9 (3.8–9.3)	<0.001	5.7 (3.8–8.5)	<0.001
5	5.2 (2.2–11.9)	<0.001	4.4 (1.6–12.2)	0.005	7.5 (4.9–11.5)	<0.001	7.4 (4.8–11.5)	<0.001

BCRFS = biochemical recurrence–free survival; CI = confidence interval; HR = hazard ratio; ref = reference.

follow-up of 4.8 yr (IQR 2.7–8.2 yr). According to the current grading system, 188 (37%) men had GG1, 154 (30%) GG2, 66 (13%) GG3, 48 (9%) GG4, and 52 (10%) GG5 Pca, corresponding to 306 (60%) cGrade1, 64 (13%) cGrade2, 59 (12%) cGrade3, 44 (9%) cGrade4, and 35 (7%) cGrade5 (Table 4). The biopsy cGrade (C-index 0.71; 95% CI 0.68–0.75) had a comparable discriminative value ($p = 0.2$) for BCRFS after RT with the GG (C-index 0.72; 95% CI 0.69–0.75).

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3.6. Eligibility for active surveillance

The most prominent effect of the cGrade model over the current GG model is the reclassification of men potentially being eligible for active surveillance. In total 272/1031 (26.4%) men fulfilled the Prostate Cancer Research International Active Surveillance (PRIAS) criteria for active surveillance (GG1, positive biopsies $\leq$2, $\leq$cT2, PSA $<$ 10 ng/ml, and PSA density $<$0.2 ng/ml^2). In case cGrade1 was used instead of GG1, the total number of patients fulfilling the PRIAS criteria increased by 84 (8.1%) to 356/1031 (34.5%) of the entire population. The effect was larger if less stringent eligibility criteria were applied. If the number of positive biopsies was not taken into account, as increasingly happens in current practice with larger numbers of systematic as well as multiparametric magnetic resonance imaging (mpMRI)-targeted biopsies, the total number of patients being eligible for active surveillance increased by 151 (14.6%), from 361 (35.0%) for GG1 to 512 (49.7%) for cGrade1.

4. Discussion

Pathological grading by GS and GG is one of the most important parameters for predicting Pca outcome and guiding clinical decision making. In the past decade, intraductal carcinoma and invasive cribriform carcinoma have both been recognised as novel pathological features with independent predictive values for adverse Pca outcome. Incorporation of these parameters in Pca grading is, however, needed to facilitate widespread implementation into clinical practice. In the current study, we demonstrate that a simple modification of the GG system with respect to the presence or absence of CR/IDC outperforms current Pca grading. In a set of over a thousand diagnostic prostate biopsies, we found that the cGrade showed a stronger discriminative value for the prediction of DSS and MFS than contemporary Pca grading.

In the past decade, the independent predictive value of additional histopathological features has been recognised. Intraductal carcinoma is a proliferation of malignant cells in pre-existent prostate glands, which has been related to an adverse disease outcome but which is not included in Gleason grading or the GG [10,11,13,16]. Invasive cribriform growth is a Gleason pattern 4 subgroup associated with worse DSS than the other Gleason 4 growth patterns [5,6,9,17,18]. Invasive cribriform and intraductal carcinoma show overlapping morphological features, and might be difficult to differentiate without the use of basal cell immunohistochemistry. Therefore, both patterns are often grouped as one entity [13,19]. Percentage Gleason pattern 4 has also been shown to have an additive prognostic value for Pca outcome [5,15]. However, we did not find any additive predictive value of Gleason pattern 4. This discordance might be explained by our analysis of percentage Gleason pattern 4 as a continuous instead of a dichotomised variable.

One of the most important weaknesses of Gleason grading is its substantial interobserver variability [20]. While interobserver variability might have minor therapeutic implications in patients with GG3–5 Pca, it has significant impact on men with GG1 and GG2 disease since their distinction commonly determines eligibility for active surveillance. Grading discordances particularly occur in differentiating poorly formed and fused Gleason pattern 4 from tangentially sectioned pattern 3 [20,21]. Interobserver agreement is, however, excellent for cribriform pattern 4, which is generally not confused with Gleason pattern 3 [20,21]. The fact that men with biopsy GG2 Pca without CR/IDC had comparable clinical outcome to those with GG1 disease, and the existence of substantial interobserver variability in distinguishing between GG1 and GG2 Pca constitute an important rationale for coalescing both groups into cGrade1 [8,9]. This is also supported by the low rate of lymph node metastases in men with GG2 Pca. Diolombi and Epstein [22] found 0.6% pelvic lymph node metastasis among 3235 men with GG2 Pca at RP without stratification for CR/IDC. In another GG2 RP cohort, lymph node metastasis were present in 12/228 (5.3%) patients with CR/IDC but in none of 192 men without CR/IDC [23]. Studies comparing the interobserver variability of both models, however, still have to be performed.

In the current study, 256 out of 310 men with biopsy GG2 disease were reclassified as cGrade1. The proportion of men fulfilling the PRIAS criteria for active surveillance increased from 26.4% to 34.5% if cGrade1 was used instead of GG1. This number further increased if less stringent eligibility criteria were used. Since upgrading is the most important parameter for surveillance discontinuation, applying the cGrade instead of GG would lead not only to a larger number of patients meeting the inclusion criteria, but also to fewer dropouts due to grade progression from GG1 to GG2 [24].

Gleason grading has been a work in progress for more than half a century. The WHO/ISUP significantly modified the Gleason grading system in 2005 and achieved minor modifications in 2014 [2,25]. While the cGrade model outperformed the current GG model, we feel that there is still room for improvement. For instance, we noted in our cohort that men with GG4 disease without CR/IDC had DSS rates comparable to those with GG2 and GG3 disease. This is in line with the findings of Harding-Jackson et al [27], who also found relatively good outcome in GG4 Pca patients without cribriform pattern. With the introduction of the GG system, all patients with GS8 are classified as GG4 Pca patients irrespective of the GS being 3 + 5, 4 + 4, or 5 + 3. Van den Bergh et al found that men with GS 3 + 5 = 8 had significantly better BCRFS than GS8 patients with any of the other grade combinations, although such a difference could not be confirmed by others [26-28]. Detailed analyses for the presence of CR/IDC in this heterogeneous population of GG4 Pca patients might further improve Pca grading. At this moment, we do not advocate to modify Pca grading. Additional improvements, reproducibility studies, and independent validations are warranted before grade modifications can be implemented with broad support of the scientific community.

The strongest point of this study is the use of a well-characterised population of Pca patients with long-term follow-up and strong clinical endpoints. The diagnostic and

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treatment modalities in the 1990s, however, were significantly different from contemporary strategies that include a larger number of biopsies, application of mpMRI, and active surveillance. Therefore, validation of the current findings in more contemporary cohorts is important before its routine adoption. We expect that the performance of the cGrade model will be even better in contemporary cohorts, since a larger number of systematic and targeted biopsies decrease biopsy sampling artefacts.

5. Conclusions

In this proof-of-principle study, we demonstrate that the biopsy cGrade is a simple modification of the GG system having better discriminative values for DSS and MFS than current Pca grading. Reclassification of GG2 Pca patients with favourable outcome as cGrade1 might allow more patients to be considered for active surveillance.

Author contributions: Geert J.L.H. van Leenders had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data: van Leenders, Nieboer, Incrocci, Bangma, van der Kwast, Roobol.
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Obtaining funding: None.
Administrative, technical, or material support: Hollemans, Verhoef, Remmers.
Supervision: van Leenders, Roobol.
Other: None.

Financial disclosures: Geert J.L.H. van Leenders certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Conflicts of interest: The authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.07.051.

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Please cite this article in press as: van Leenders GJLH, et al. Improved Prostate Cancer Biopsy Grading by Incorporation of Invasive Cribriform and Intraductal Carcinoma in the 2014 Grade Groups. Eur Urol (2019), https://doi.org/10.1016/j.eururo.2019.07.051